REMARKS

Claims 1 and 6-13 are pending. Claim 2 is cancelled and new claims 26-30 are presented. No new matter is added by the new claims and the new claims are supported by the application as filed. New claim 26 is supported by original claim 2. New claim 27 is supported by the specification, for example, specification, Examples 3-5 and Tables 3-5. New claim 28 is supported by the specification as filed which contemplates using the free acid of ibuprofen. The application provides the structure for the free acid form of ibuprofen. (*See* specification, page 3). In contrast, the application describes salt forms of diphenydramine, including diphenhydramine citrate and diphenhydramine HCl and provides chemical structures of those compounds. (See e.g., claim 9, and specification, page 5). When describing formulations of the instant invention, the specification consistently uses the term "ibuprofen" but describes specific salt forms of diphenhydramine. (*See*, specification, from page 10, line 16 to page 11, line 9. Also see, specification, page 15, line 1 and line 11). In the working examples, the term "ibuprofen" is used while diphenydramine salts are described (See Examples 1 and 2, and Tables 1 and 2). Claim 30 is supported by the specification, page 15, lines 2-10.

Applicants respectfully request consideration and examination of this application and the timely allowance of the pending claims in view of the arguments below.

Obviousness Rejections Under 35 USC § 103

Rejection of Gel Capsule Claims

The Office maintains its rejection of claims 2 and 6-13 as allegedly unpatentable over U.S. Patent No. 4,522,826 ("*Sunshine*") in view of U.S. Patent No. 5,431,916 ("*White*"). The Office continues to assert that *Sunshine* teaches that polyethylene glycol "is a suitable binder to be employed in the composition comprising ibuprofen and diphenhydramine and additionally White also teaches that polyethylene glycol is suitable in the composition comprising ibuprofen and diphenhydramine." Office action, 12/20/2005, p. 3. The Office concludes that one of ordinary skill in the art would be motivated to select polyethylene glycol for inclusion in a composition comprising ibuprofen and diphenhydramine. *Id.* at 3-4.

The rejection of claim 2 is moot in light of Applicant's cancellation of claim 2. Applicants respectfully traverse the obviousness rejection of claims 6-13. A proper *prima facie* obviousness rejection requires some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. The Examiner bears the burden of establishing *prima facie* obviousness. *See* M.P.E.P. § 2142.

The Examiner has failed to establish *prima facie* obviousness as the documents cited by the Office fail to provide motivation to modify or combine reference teachings.

In particular, no motivation is provided for selecting polyethylene glycol, which appears in a laundry list of compounds in *Sunshine*, and both *Sunshine* and *White* teach away from inclusion of polyethylene glycol in a composition comprising ibuprofen and diphenhydramine.

The mere mention of polyethylene glycol in *Sunshine* does not render the instant invention obvious. As recognized by the Federal Circuit "virtually all inventions are combinations of old elements . . . . If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue." *See*, for example, *In re Rouffet*, 149 F.3d 1350, 1356, 47 U.S.P.Q.2d 1453, 1459 (Fed. Cir. 1998). Moreover, a prior art reference containing a "needle-in-the-haystack" type disclosure does not render a patent obvious. *See*, for example, *In re Luvisi*, 342 F.2d 102, 105, 144 U.S.P.Q. 646, 649 (C.C.P.A. 1965) ("Luvisi"). In *Luvisi*, the court reversed the Board's finding of obviousness because there was nothing in the references relied on by the Examiner that would suggest the selection of one compound from a list of around fifty compounds. *Id.*

In *Sunshine*, polyethylene glycol is one compound in a laundry list of "[s]uitable binders" including the following species and *genuses*:

> *starch*, gelatin, *natural sugars*, corn sweeteners, *natural and synthetic gums* such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and *waxes*.

Sunshine, col. 7, lines 30-33 (emphasis added). This laundry list includes several genuses of binders (e.g., starch, waxes, natural sugars, corn sweetners, natural and synthetic gums) and specific species (e.g., sodium alginate, polyethylene glycol).

These genuses are very large, and include both the compounds mentioned in *Sunshine*, as well as members of the genus recognized by the skilled artisan, including at least the:

- FDA approved starches: carboxymethyl starch, sodium starch glycolate, starch, starch 1500 pregelatinized, starch 1551, corn starch, pregelatinized starch, pregelatinzed corn starch, potato starch, pregelatinzed tapioca starch, rice starch, tapioca starch, and wheat starch;
- the waxes: carnauba wax, wax blend, emulsifying wax, dehydag wax, microcrysalline wax, white wax, yellow wax, beeswax, synthetic beeswax, and candelilla wax;
- the natural sugars: dextrose, high fructose corn syrup, and sucrose; and
- the gums: guar gum, rosin gum, natural gum and xanthan gum.

Inactive Ingredient Guide, Division of Drug Information Resources, Food and Drug Administration (1996). Moreover, known "binders" include

- the FDA approved binders alginic acid, cellulose, hydroxyethylcellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyethylene oxide.

Id. There is no suggestion in *Sunshine* that polyethylene glycol should be chosen from this extensive list of compounds, the kind of "needle in the haystack" disclosure held insufficient to support an obviousness rejection in *Luvisi*. Accordingly, the mere mention of polyethylene glycol in *Sunshine* does not render the instant invention obvious

because *Sunshine* does not provide the motivation to select polyethylene glycol required for *prima facie* obviousness.

Sunshine not only fails to provide motivation to select polyethylene glycol, *Sunshine* actually teaches away from inclusion of polyethylene glycol. *Sunshine* teaches compositions containing ibuprofen and diphenhydramine but lacking polyethylene glycol. For example, a solution of ibuprofen, diphenhydramine and methylcellulose is described in Example 1. Moreover, the compositions described in the claims of *Sunshine* do not recite polyethylene glycol, or any other binder. Finally, the benefits of polyethylene glycol in a composition comprising ibuprofen and diphenhydramine were not contemplated in *Sunshine*. Therefore, *Sunshine* not only fails to motivate one skilled in the art to select polyethylene glycol from the laundry list of compounds it describes, it teaches compositions containing ibuprofen and diphenhydramine that lack polyethylene glycol.

White fails to compensate for the lack of motivation in *Sunshine* to select polyethylene glycol, because like *Sunshine*, it teaches away from the instant invention. *White* states that, "[p]revious solvent systems utilized common solvents such as propylene glycol and polyethylene glycols; each providing excellent solvency <u>but neither being completely appropriate</u> for an important category of pharmaceutically acceptable active agents, the nonsteroidal anti-inflammatory compounds." *White*, col. 1, line 66 to col. 2, line 4. (emphasis added). Accordingly, *White* teaches that polyethylene glycol is not a desired compound for use with NSAIDs and one skilled in the art would be dissuaded from using polyethylene glycol with ibuprofen and diphenhydramine.

Consistent with this teaching, the sole example in *White* of a composition containing ibuprofen and diphenhydramine lacks polyethylene glycol. *White*, Example IV. *White* further teaches away from polyethylene glycol as merely an "optional component that may be used to solubilize certain pharmaceutical actives." *White*, col. 6, line 41. In fact, *White* describes polyethylene glycol as useful to "facilitate dissolution of highly water soluble pharmaceutically acceptable actives that have modest to low solubility in the tri-ester component of the present invention." Column 7, lines 24-28. Therefore, the only teaching of *White* that suggests an advantage of polyethylene glycol is to enhance solubility in the tri-esters of *White* and the only claim of *White* that includes polyethylene glycol, claim 15, is directed to the use of either polyethylene glycol or water in a composition containing a tri-ester. *White* does not contemplate the advantages of polyethylene glycol for preventing the negative interaction between ibuprofen and diphenhydramine disclosed in the instant application. One of ordinary skill in the art would not be motivated by *White* to include polyethylene glycol in a composition comprising ibuprofen and diphenhydramine, unless the composition contained a tri-ester, a component that is not required in composition of any of the instant claims. Accordingly, *White* does not teach or suggest the subject matter of claims 6-13, and fails to provide the motivation for the selection of polyethylene glycol lacking from *Sunshine*.

The Office states that "Sunshine et al. do not teach the composition formulated in a soft gelatin capsule" but appears to rely on *White* for providing the motivation to use the claimed composition in soft gelatin capsules. Office action, 12/20/2005, p. 6. As

described in detail above, *White*, either alone or when combined with *Sunshine*, fails to specifically disclose a composition comprised of ibuprofen, diphenhydramine and polyethylene glycol, *White* provides no motivation to make such a composition, and actually teaches away from such a composition. Additionally, *White* does not teach or suggest formulating this composition in a soft gelatin capsule. In fact, the sole example in *White* of a soft gelatin capsule containing ibuprofen and diphenhydramine lacks polyethylene glycol. *White*, Example IV. Accordingly, *White* would not motivate one of ordinary skill in the art to formulate a composition which contains ibuprofen, diphenhydramine and polyethylene glycol in a soft gelatin capsule as *White* neither teaches such a composition nor teaches the composition formulated in a soft gelatin capsule.

Applicants submit that *Sunshine* and *White* provide no motivation to arrive at the claimed composition comprising ibuprofen, diphenhydramine and polyethylene glycol and actually teach away from the inclusion of polyethylene glycol. Furthermore, *White* provides no motivation to formulate such a composition in a soft gelatin capsule. In view of the foregoing, Applicants respectfully request that the rejection of claims 2-6 be withdrawn.

Rejection of Bilayer Tablet Claims

The Office also maintains the rejection of claims 1, 2 and 7-13 as allegedly unpatentable over *Sunshine* in view of U.S. Patent No. 5,512,300 ("*Weng*") and further in view of U.S. Patent No. 6,287,600 ("*Ouali*"). *Id.* at 4. The Office alleges that it would have been obvious for one of ordinary skill in the art to separate diphenhydramine and

ibuprofen of *Sunshine* in a bilayer tablet because *Weng* teaches that such a composition has stability problems and *Ouali* provides the motivation to use a bilayer tablet to physically separate the two. *Id.* at 6.

The rejection of claim 2 is moot in light of Applicant's cancellation of claim 2. Applicants respectfully traverse the obviousness rejection of claims 1 and 7-13. Applicants submit that the Office has failed to provide any motivation in any of the references to modify or combine their teachings. As stated by the Office, "Sunshine *et al.* do not teach the separation of ibuprofen and diphenhydramine in bilayer tablet formation." *Id.* at 7. *Weng* and *Ouali* do not cure the deficiencies of *Sunshine*. *Weng* discusses methods for preparing ibuprofen granulations which exhibit improved stability and resistance to the formation of low melting point eutectics. *See* Abstract. *Weng*, however, fails to teach or suggest separating ibuprofen from another substance and focuses on preparing stabilized ibuprofen through chemical treatment. Therefore, based on *Weng*, one of ordinary skill in the art might be motivated to use chemically treated ibuprofen in combination with diphenhydramine, but not a bilayer tablet to separate the two. In fact, because *Weng* provides a potential solution to the problem of low melting point eutectics formed in mixtures of ibuprofen and diphenhydramine, one of ordinary skill in the art would not be motivated to solve this problem through use of a bilayer tablet.

Weng also fails to teach or suggest the instantly claimed invention because the method of chemically treating ibuprofen taught be *Weng* produces a salt from of ibuprofen. (*See* abstract of Kararli *et al.* "Solid State Interaction of Magnesium Oxide

and Ibuprofen to Form a Salt," Pharm. Res. 6: 804-808 (1989)), cited on the face of *Weng*, which teaches that mixing magnesium oxide and ibuprofen results in formation of an ibuprofen-magnesium salt).

The specification uses the term "ibuprofen" to indicate that the free acid is contemplated. The application provides the structure for the free acid form of ibuprofen. (*See* specification, page 3). The formulations of the instant invention use "ibuprofen" in combination with specifically named salt forms of diphenhydramine. (*See* specification, from page 10, line 16 to page 11, line 9. Also see, specification, page 15, line 1 and line 11). In the working examples, the term "ibuprofen" is used while diphenydramine salts are described (*See* Examples 1 and 2, and Tables 1 and 2). Accordingly, the method for treating ibuprofen discussed in *Weng* does not suggest the claimed composition which uses the ibuprofen free acid.

Weng fails to contemplate the advantages of ibuprofen free acid over salt forms. Ibuprofen free acid is more chemically stable than salt forms during manufacture. The salt forms are hydrated and can change hydration states resulting in changed physical and chemical stability in dosage form. This sample of some of the advantages to the free acid form of ibuprofen establishes that one of skill in the art would not be motivated to use the composition of *Weng* to arrive at the claimed composition. Therefore, one skilled in the art would not have an expectation of success in making the claimed invention with an ibuprofen salt because of the disadvantages of ibuprofen salts.

The Office appears to rely on *Ouali* as providing the motivation to separate the ibuprofen from diphenhydramine. *Ouali* discusses the advantage of a composition

containing an NSAID and a prostaglandin, but teaches that prostaglandins are unstable compounds that degrade in the presence of NSAIDs. *Ouali*, col. 1, line 59. However, *Ouali* does not teach that a bilayer is tablet is sufficient to solve the problem caused by a mixture of an NSAID and a prostaglandin, but teaches that enteric coating of the NSAID solves the problem. The bilayer tablets of *Ouali* are "comprised of two discrete regions, wherein the enterically coated NSAID is present in a first region..." col. 4, line 1. *Ouali* further states that "The NSAID is enterically coated within the stabilized composition of the invention." col. 4, line 52. The steps for manufacturing the tablets state that "[o]nce in particulate form, the NSAID is enterically coated," prior to incorporation in the dosage form. *Ouali*, col. 7, line 18. *Ouali* actually teaches that the enteric coating solves the problem of the interaction between the NSAID and the prostaglandin and that a bilayer tablet is not even necessary.

> In an alternative embodiment, the enterically coated NSAID and the stabilized prostaglandin are mixed into a single granulation, and the admixture is compressed into a tablet or filled into a capsule. In the admixture, there is a random possibility of the NSAID and the prostaglandin coming into contact with each other. However, the enteric coating on the NSAID granules provides a physical barrier between the NSAID and the prostaglandin, thereby minimizing direct physical contact between the two active agents.

Ouali, col. 7, line 51.

Therefore, *Ouali* teaches that the interaction between an NSAID and prostaglandin is prevented by the enteric coating. In fact, if the bilayer tablet formulation of *Ouali* was made by pressing a layer comprised of non-coated NSAID with a layer comprised of prostaglandin, there would still be potential for the NSAID to induce

degradation of the prostaglandin at the interface of the two layers. However, because the NSAID is coated, *Ouali* teaches that such a negative interaction would be prevented. In other words, *Ouali* teaches enterically coating an NSAID would solve the problem of prostaglandin degradation. What *Ouali* does not teach is that merely separating the NSAID from the prostaglandin in a bilayer tablet is a suitable solution, as the working examples of *Ouali* all use an enterically coated NSAIDs . In fact, the only stated advantages of a bilayer tablet are "manufacturing advantages." *Ouali*, col. 7, line 30. There is no teaching or suggestion in *Ouali* that these supposed manufacturing advantages would even apply to the composition of the instant invention. Accordingly, if one skilled in the art were motivated to combine the teaching of *Ouali* with that of *Sunshine* or *Weng*, one would arrive at a composition in which the NSAID is enterically coated, which is not a requirement of claims 1 or 7-13. In fact, the instant invention does not favor enteric coating.

The instant invention is directed in part toward addressing the need in the art for compositions allowing a person to fall asleep more rapidly (*See* specification, page 2, line 18). The rapidly acting compositions of the claimed invention are based on the pharmacokinetic profile of ibuprofen. (*See* specification, from page 16, line 20 to page 17, line 1). Patients administered the composition of the instant invention exhibited improvement in "cumulative percent asleep at 60 minutes, ease of falling asleep, duration of sleep, and global evaluation," and the results on sleep duration were surprising. (*See* specification, page 29, lines 9-11, Examples 3-5 and Tables 3-5).

Ouali teach that coating the NSAID results in a composition that releases the drug in the intestine, but remains intact in the stomach. (*See*, column 3, lines 29-32 and column 4, lines 52-58). Therefore, the effect of enterically coated NSAIDs is delayed by the additional time required for the NSAID to pass from the stomach to the intestine. Thus, *Ouali* does not suggest a solution to the problem of *Weng*, as one of skill in the art wishing to make a rapidly acting composition would not formulate the ibuprofen in a manner that could delay its effect in rapidly inducing sleep when combined with diphenhydramine. Thus, the enteric coating of *Ouali* would prevent the desired rapid action profile of the present invention.

Applicants submit that *Sunshine*, *Weng* and *Ouali* provide no motivation to arrive at the claimed composition which contains all three of ibuprofen, diphenhydramine and polyethylene glycol in a bilayer tablet as they teach coating or chemical modification of an NSAID. In view of the foregoing, Applicants respectfully request that the rejection of claims 1 and 7-13 be withdrawn.

Conclusion

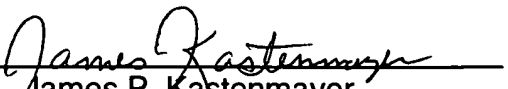
In view of the foregoing, Applicants submit that claimed invention is not obvious in view of the cited art and that the pending claims are in condition for allowance. Applicants request reconsideration and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 20, 2006

By: 
James P. Kastenmayer
Reg. No. 51,862